

CLAIMS

1. Compounds of general formula (E) below :



5. in which:

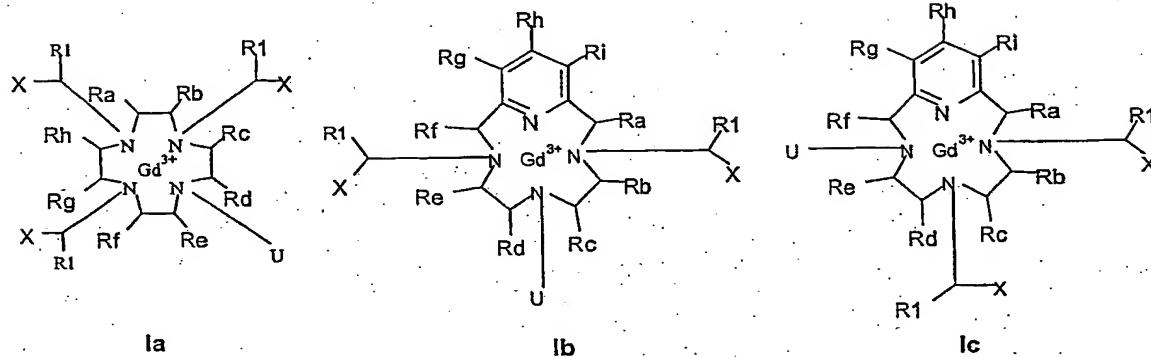
- B is a biovector
- L is a linker
- HR Ch represents a chelate of formula (I):



10 with :

a) $I_{a,b,c,d,e,f,g}$ chosen from $I_a, I_b, I_c, I_d, I_e, I_f, I_g$.

I_a, I_b, I_c having the meanings :



where :

- the X, which may be identical or different, are chosen from $\text{CO}_2\text{R}'_a$, $\text{CONR}'_b\text{R}'_c$ or $\text{P}(\text{R}'_d)\text{O}_2\text{H}$, with :
 - R'_a , R'_b and R'_c , which may be identical or different, representing H or $(\text{C}_1\text{-}\text{C}_8)$ alkyl, which is optionally hydroxylated ;
 - P is the phosphorus atom, R'_d is chosen from OH, $(\text{C}_1\text{-}\text{C}_8)$ alkyl or $(\text{C}_1\text{-}\text{C}_8)$ alkoxy, $(\text{C}_1\text{-}\text{C}_8)$ arylalkyl or $(\text{C}_1\text{-}\text{C}_8)$ alkoxyalkyl ;

- R₁ represents a hydrophilic group of molecular weight greater than 200, selected from groups :

- polyoxy(C₂-C₃)alkylene, in particular polyethylene glycol and its C₁-C₃ monoethers and monoesters, preferably of molecular mass from 1000 to 2000
- polyhydroxyalkyl
- polyol
- (R₂g)_e[(R₂g)_iR₃]_h where:

- h = 1 or 2 ; i = 0, 1 or 2 ; e = 1 to 5

- R₂ represents (the R₂ being identical or different) :

- nothing, an alkylene, an alkoxyalkylene, a polyalkoxyalkylene;
- a phenylene, or a heterocyclic residue which may be saturated or unsaturated, optionally substituted with OH, Cl, Br, I, (C₁-C₈)alkyl, (C₁-C₈)alkyloxy, NO₂, NR_xR_y, NR_xCOR_y, CONR_xR_y or COOR_x, R_x and R_y being H or (C₁-C₈)alkyl, and the linear, branched or cyclic C₁-C₁₄ alkyl, alkylene and alkoxy groups possibly being hydroxylated ;

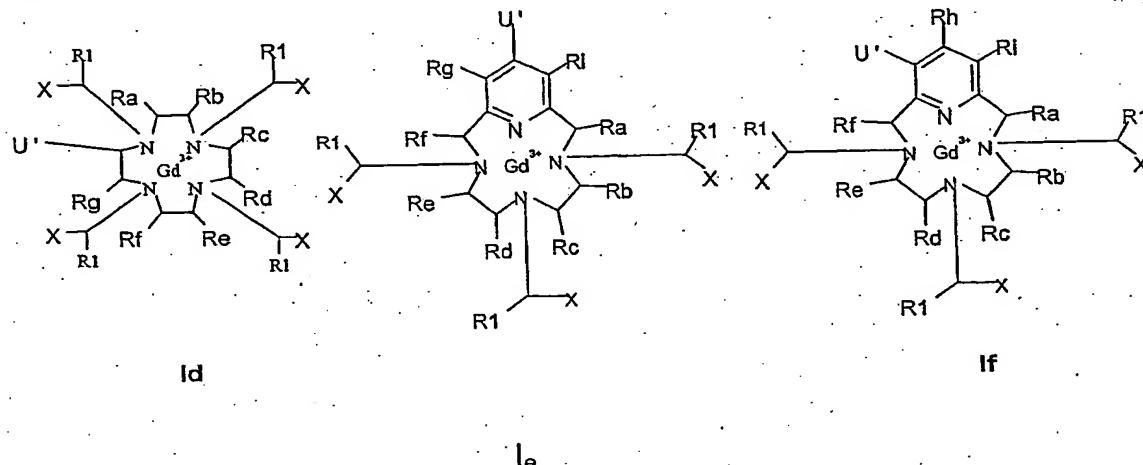
- g represents (the g being identical or different): nothing or a function O, CO, OCO, COO, SO₃, OSO₂, CONR', NR'CO, NR'COO, OCONR', NR', NR'CS, CSNR', SO₂NR', NR'SO₂, NR'CSO, OCSNR', NR'CSNR', P(O)(OH)NR', NR'P(O)-(OH), in which R' is H, (C₁-C₈)alkyl or R₃;

- R₃ represents alkyl, phenyl, alkyl substituted or interrupted with one or more phenyl groups, alkyleneoxy groups; amino or amido unsubstituted or substituted with alkyl optionally substituted or interrupted with one of the above groups; phenyl, phenylene and heterocyclic groups which may be substituted with OH, Cl, Br, I,

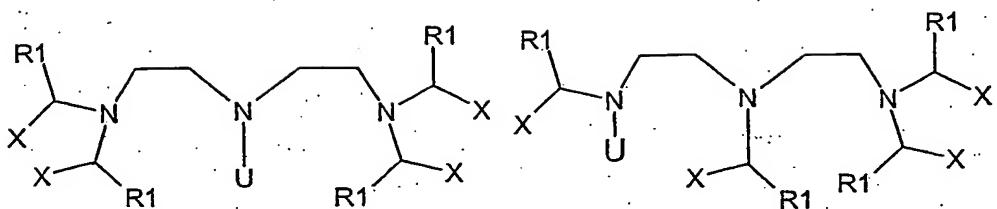
(C₁-C₈)alkyl, (C₁-C₈)alkyloxy, NO₂, NR_xR_y, NR_xCOR_y, CONR_xR_y or COOR_x, R_x and R_y being H or (C₁-C₈)alkyl, and linear, branched or cyclic C₁-C₁₄ alkyl, alkylene and alkoxy groups which may be hydroxylated;

- 5 - R_a to R_i independently represent H, alkyl, hydroxyalkyl, alkylphenyl or cycloalkyl;
- U is a group -CXR₄-linker 1, CHR₄CON-linker 1, CHR₄-CHR₅OH-linker 1
- R₄ and R₅ independently representing H, alkyl or hydroxyalkyl,
- 10 - X having the meaning above,
- linker 1 being the linker providing the link between a chelate I_{a, b, c}, and the linker L when q=0 and between I_{a, b, c}, and D when q=1

15 I_d, I_e, I_f having the meanings :



- 20 - X, R1, Ra to Ri having the same meaning as above,
- U' is linker 1, providing the link between a chelate I_{d,e,f} and a linker L when q=0 and between I_{d,e,f} and D when q=1,
- I_g representing



U, X, R1 having the same meaning as above, linker 1 providing the link between a chelate I_g and a linker L when $q=0$ and between I_g and D when $q=1$.

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b)

- $q = 0$ or $q=1$ - $r=1$ when $q=0$, or r is between 2 and 5 when $q=1$

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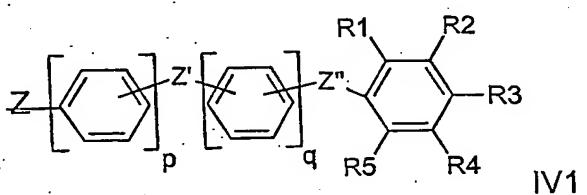
c) D is a polyfunctional molecule capable of linking a linker L to at least two chelates $I_{a,b,c,d,e,f,g}$

15

and also the salts of the compounds of formula (E) with pharmaceutically acceptable inorganic or organic acids or bases.

2. Compound according to Claim 1, characterized in that R1 is
20 $(CH_2)_xCONHR$ with $x=1, 2$ or 3 and R is a hydrophilic group of molecular weight greater than 200, chosen from :

1) a group:



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and Z is a bond, CH_2 , CH_2CONH or $(CH_2)_2NHCO$

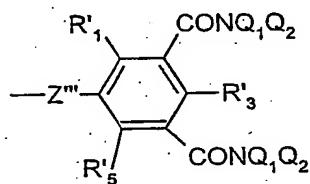
Z' is a bond, O, S, NQ, CH₂, CO, CONQ, NQCO, NQ-CONQ or CONQCH₂CONQ,

Z" is a bond, CONQ, NQCO or CONQCH₂CONQ

p and q are integers, the sum of which is 0 to 3 ;

5 R₁, R₂, R₃, R₄ or R₅ represent:

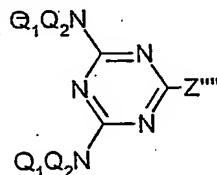
- either, independently of one another, H, Br, Cl, I, CONQ₁Q₂ or NQ₁COQ₂ with Q₁ and Q₂, which may be identical or different, being H or a (C₁-C₈)alkyl group which is mono- or polyhydroxylated or optionally interrupted with one or more oxygen atoms, and at least one and no more than two of R₁ to R₅ are CONQ₁Q₂ or NQ₁COQ₂ ;
- or R₂ and R₄ represent



10 and R₁, R'₁, R₃, R'₃, R₅ and R'₅, which may be identical or different, represent H, Br, Cl or I, Q₁ and Q₂ have the same meaning as above and Z''' is a group chosen from CONQ, CONQCH₂CONQ, CONQCH₂, NQCONQ and CONQ(CH₂)₂NQCO and Q is H or (C₁-C₄)alkyl, which is optionally hydroxylated, it being possible for the alkyl groups to be linear or branched ;

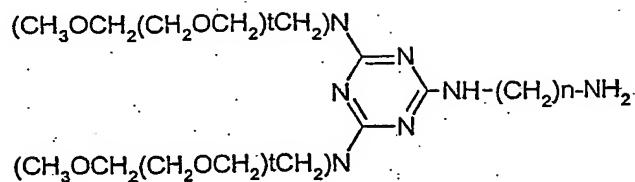
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20 2) a "flash" branch

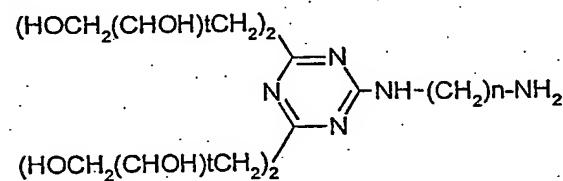


with Z''' being NQ(CH₂)_i(CH₂OCH₂)_j(CH₂)_kNH₂ with i = 2 to 6 and j = 1 to 6,

preferably



or

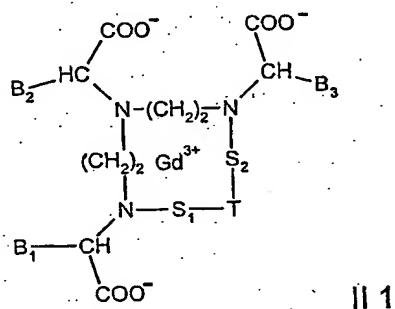


5 with $\text{t} = 1, 2, 3$ or 4 and $n = 2$ to 6 .

3. Compound according to Claim 1 or 2, characterized in that $q = 1$.

4. Compound according to Claim 1 or 2, characterized in that HR Ch

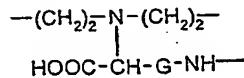
10 represents the group:



in which :

$-\text{S}_1-\text{T}-\text{S}_2-$ is

1) either



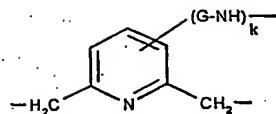
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where $\text{S}_1 = \text{S}_2 = (\text{CH}_2)_2$

with all three of B_1 , B_2 and B_3 representing $(\text{CH}_2)_x\text{CONHR}$ with

$x = 1, 2$ or 3

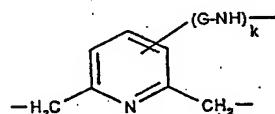
2) or



III1

with $k = 0$ and $S_1 = S_2 = CH_2$ 5 one of B_1, B_2, B_3 representing $G-NH$, and the othersrepresenting $(CH_2)_xCONHR$

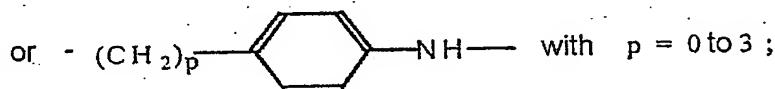
3) or



III1

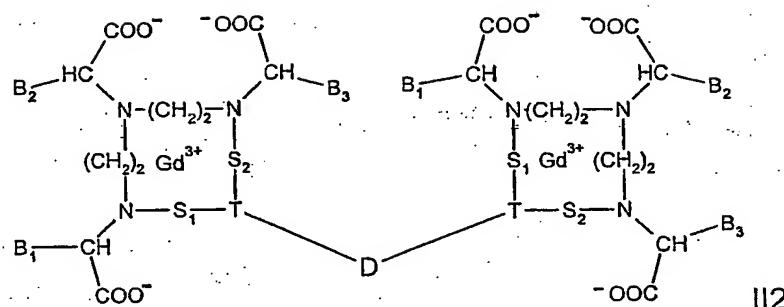
with $k=1$ all three of B_1, B_2, B_3 representing $(CH_2)_xCONHR$ with $x = 1$,

2 or 3

15 and GNH chosen from :the groups $-(CH_2)_n-NH-$ with $n = 1$ to 4,5. Compound according to Claim 3, characterized in that HR Ch

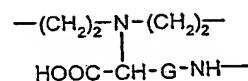
20 represents a group chosen from :

1) the group



in which

-S₁-T-S₂- is

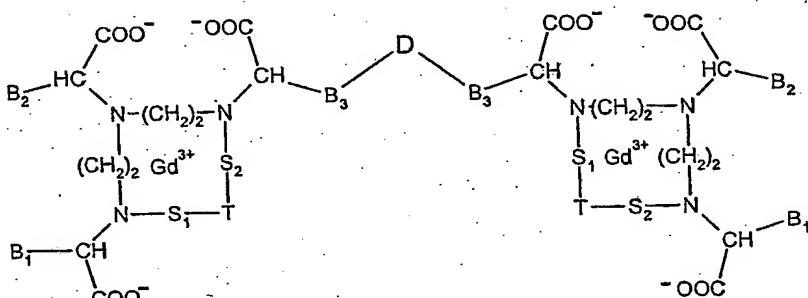


where S₁ = S₂ = (CH₂)₂

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all three of B₁, B₂, B₃ representing (CH₂)_xCONHR with x = 1, 2 or 3

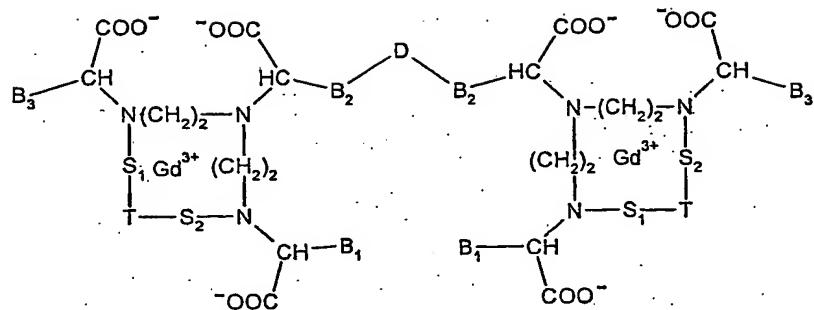
2) the group



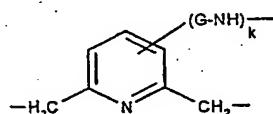
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IIa2 (compound referred to as N-functionalized PCTA)

or IIb2 (compound referred to as N-functionalized PCTA and positional isomer of IIa2)



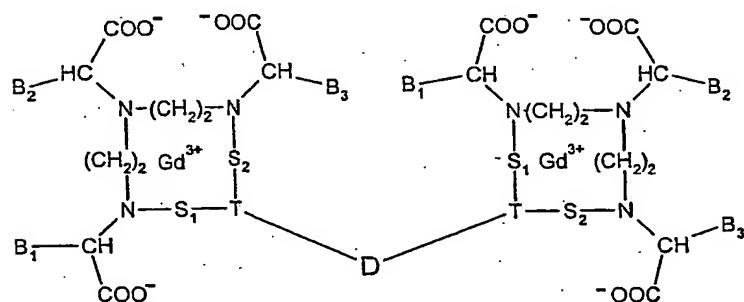
IIb2

5. in which S_1-T-S_2- is:

III2

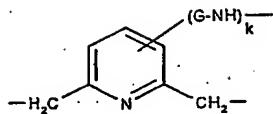
with $k = 0$ and $S_1 = S_2 = CH_2$;10 B_3 representing $G-NH$, and $B1$ and $B2$ representing $(CH_2)_xCONHR$ for IIa2 B_2 representing $G-NH$, and $B1$ and $B3$ representing $(CH_2)_xCONHR$ for IIb2

15 3) the group



IIc2 (compound referred to as C-functionalized PCTA)

when S_1-T-S_2- is :



III2

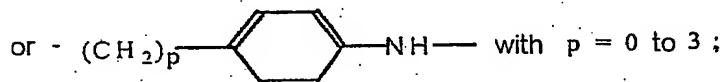
5 with $k = 1$ and $S_1 = S_2 = CH_2$;

all three of B_1, B_2, B_3 representing $(CH_2)_xCONHR$ with $x = 1, 2$ or 3

for IIc2

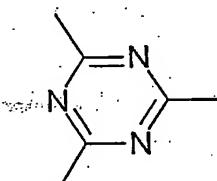
10 given that, for II2, IIa2, IIb2 and IIc2,

GNH is chosen from the groups $-(CH_2)_n-NH-$ with $n = 1$ to 4 ,



15 6. Compound according to any one of Claims 1 to 5, characterized in that
D is an aromatic backbone polyfunctionalized with carboxylate and/or
amino groups, D preferably being of 1,3,5-triazine type, of formula :

linker 2

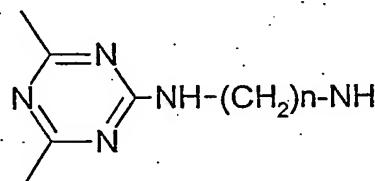


with linker 2 chosen from a) and b) and preferably a) :

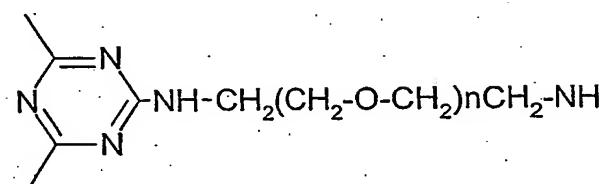
20 a) $(CH_2)_2 - \phi - NH_2$, $(CH_2)_3 - NH_2$, $NH-(CH_2)_2-NH$, $NH-(CH_2)_3-NH$,
b) P1-I-P2, which may be identical or different, P1 and P2 being
chosen from OH, SH, NH₂, nothing, CO₂H, NCS, NCO, SO₃H,

with I = alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene,

and D being more preferably :



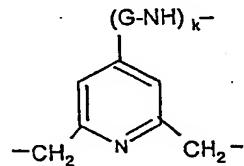
or



7. Compound according to any one of Claims 1 to 6, characterized in that
 10 L is a linker chosen from polyoxyalkylenes, squaric acid, a squareate-PEG radical, an alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene.

8. Compound according to any one of Claims 3 to 7, in which x of
 15 $(\text{CH}_2)_x\text{CONHR}$ is 2.

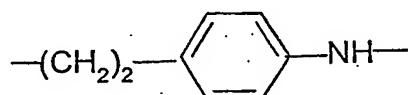
9. Compound according to any one of Claims 4 to 8, in which $-\text{S}_1-\text{T}$
 - S_2- represents:



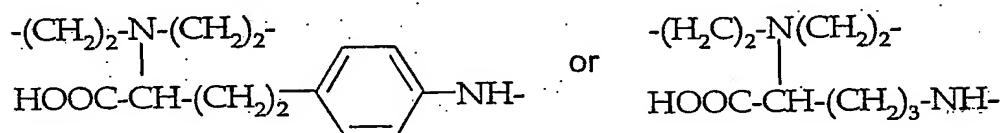
20 with $\text{S}_1 = \text{S}_2 = \text{CH}_2$.

10. Compounds according to Claim 9 of formula II1 in which k is 1 and
 G is $-(\text{CH}_2)_3-$.

11. Compounds according to Claim 9 of formula II1 in which k is 0 and B₂ or B₃ represents -(CH₂)₃NH- or



12. Compound according to any one of Claims 4 to 9, in which -S₁ - T
5 - S₂- represents:



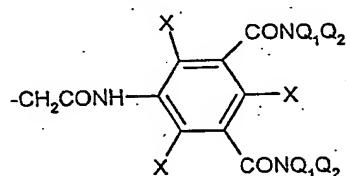
with S₁ = S₂ = (CH₂)₂.

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13. Compounds according to any one of the preceding claims, for which B₁, B₂ and B₃, when they do not represent -G-NH, represent -(CH₂)₂CONHR, with, in R, p = q = 0 and Z being -CH₂CONH.

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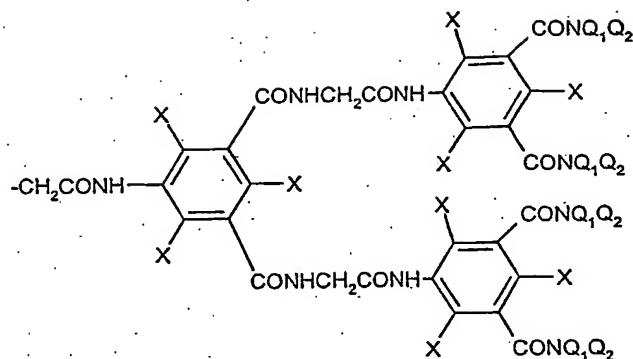
14. Compounds according to Claim 13, for which R represents:



and the X are identical and represent Br or I, while Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ contains from 4 to 10 hydroxyls in total.

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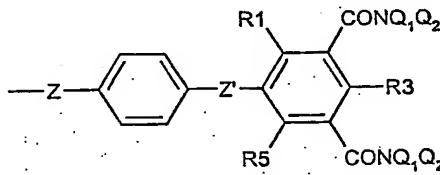
15. Compounds according to Claim 13, for which R represents:



and the X, which are identical, are Br or I; and Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ group contains from 4 to 10 hydroxyls in total.

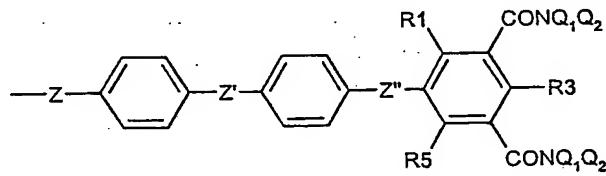
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16. Compounds according to any one of Claims 1 to 12, for which R represents:



10 Z is CH₂ or CH₂CONH, Z' is CONH or CONHCH₂CONH, R₁, R₃ and R₅, which are identical, are Br or I, and Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ group contains from 4 to 10 hydroxyls in total.

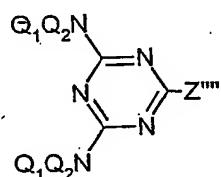
15 17. Compounds according to any one of Claims 1 to 12, for which R represents:



Z is CH_2CONH , Z' is CONH , Z'' is $\text{CONHCH}_2\text{CONH}$ and R_1 , R_3 and R_5 , which are identical, are Br or I, and Q_1 and Q_2 , which may be identical or different, are monohydroxylated or polyhydroxylated (C_1 - C_8)alkyl groups such that each CONQ_1Q_2 group comprises from 4 to 10 hydroxyls in total.

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18. Compounds according to any one of Claims 1 to 12, for which R represents

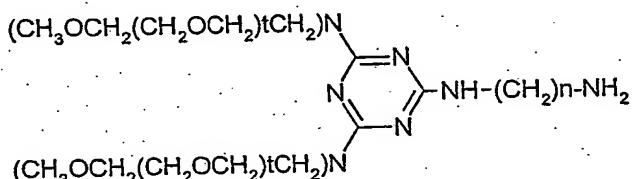


with Z''' being $\text{NQ}(\text{CH}_2)_j(\text{CH}_2\text{OCH}_2)_i(\text{CH}_2)_l\text{NH}_2$, with $i = 2$ to

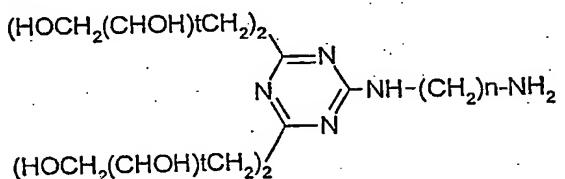
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6 and $j = 1$ to 6,

preferably R represents:



or



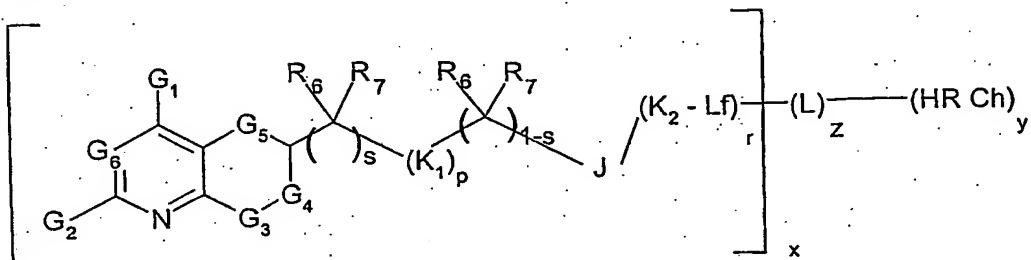
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with $t = 1, 2, 3$ or 4 and $n = 2$ to 6.

19. Compound according to one of Claims 1 to 18, characterized in that the biovector is an agent capable of targeting cellular receptors or tissue components, in particular chosen from receptors of myocardial cells, of endothelial cells, of epithelial cells, of tumour cells or of immune system cells.

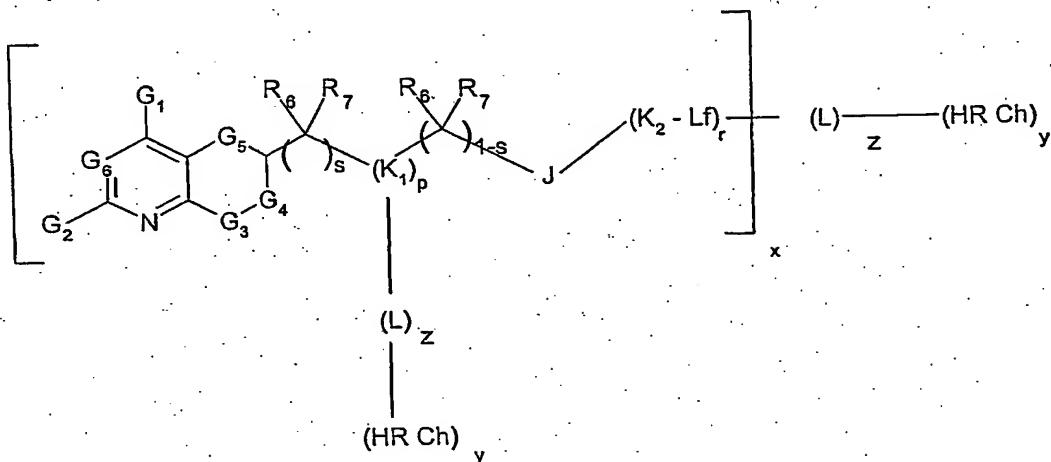
20. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting a folate receptor, (E) being written :

(E1) :



5

or (E2) :



with :

- a) G1 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, N R_f4 R_f5 ;
- 10 b) G2 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, and N R_f4 R_f5 ;
- c) G3 and G4 represent divalent groups chosen independently from the group consisting of -(R_f6') C=,-N=,-(R_f6') C (R_f7')-, -N (R_f4')- ;
- 15 d) G5 is absent or chosen from -(R_f6') C=,-N=,-(R_f6') C (R_f7')-, -N (R_f4')- ;
- e) the ring J is a possibly heterocyclic aromatic 5- or 6-membered ring, it being possible for the atoms of the ring to be C, N, O, S ;
- f) G6 is N or C ;

g) K1 and K2 are chosen independently from the group consisting of - C (Z_f)-, -C (Z_f) O, -OC (Z_f)-, -N (R_f4")-, -C (Z_f)-N (R_f4")-, -N (R_f4")-C (Z_f)-, -O-C(Z)-N(R_f4")-, -N(R_f4")-C(Z_f)-O-, N(R_f4")-C(Z_f)-N(R_f5")-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R_f4")S(O)₂-,

5 -N(C ≡ CH)-, -N(CH₂-C ≡ CH)-, C₁-C₁₂ alkyl and C₁-C₁₂ alkoxy; in which Z_f is O or S ; preferably K1 is -N(R_f4")- or -C(R_f6") (R_f7")- with R_f4", R_f6", R_f7" being H ; K2 possibly being covalently bonded to an amino acid ;

h) R_f1 is chosen from the group consisting of : H, halo, C₁-C₁₂ alkyl and C₁-C₁₂ alkoxy ; R_f2, R_f3, R_f4, R_f4', R_f4", R_f5, R_f5", R_f6" and R_f7" are chosen independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, C,-C, 2 alkanoyl, C,-C, 2 alkenyl, C₁-C₁₂ alkynyle, (C₁-C₁₂ alkoxy)carbonyl and (C,-C, 2 alkylamino)carbonyl;

10 i) R_f6 and R_f7 are chosen independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy; or R_f6 and R_f7 together form O= ;

j) R_f6' and R_f7' are chosen independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy ; or R_f6' and R_f7' together form O= ;

15 k) L_f is a divalent linker which includes, where appropriate, a natural amino acid or a natural poly(amino acid), this acid or polyacid being bonded to K2 or to K1 via its alpha-amino group via an amide bond ;

l) n, p, r and s are independently 0 or 1.

21. Compound according to Claim 20, characterized in that G1 is NH₂ or OH.

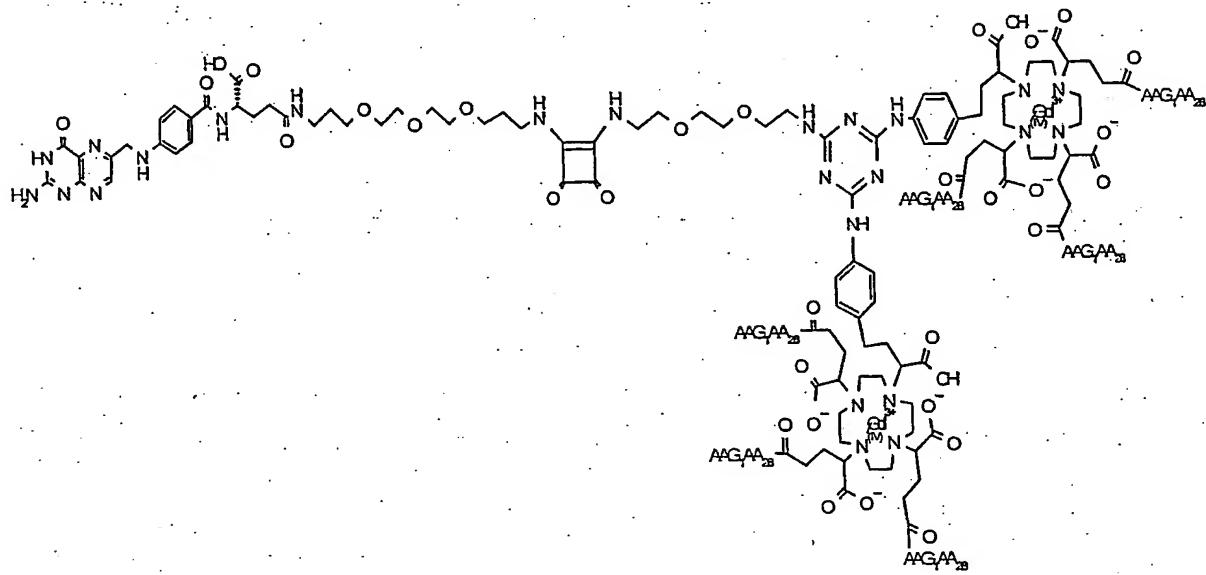
22. Compound according to Claim 20, characterized in that G3 is -N= or -CH- when the ring comprising G3 is aromatic, and G3 is -NH- or -CH₂- when the ring comprising G3 is non-aromatic ; with, preferably, G3 being -CH-, G1 being OH, G6 being NH and K1 being -N(R_f4")-.

23. Compound according to Claim 20, characterized in that G4 is $-\text{CH-}$ or $-\text{C}(\text{CH}_3)\text{-}$ when the ring comprising G3 is aromatic, and $-\text{CH}_2\text{-}$ or $-\text{CH}(\text{CH}_3)\text{-}$ when the ring comprising G3 is non-aromatic.

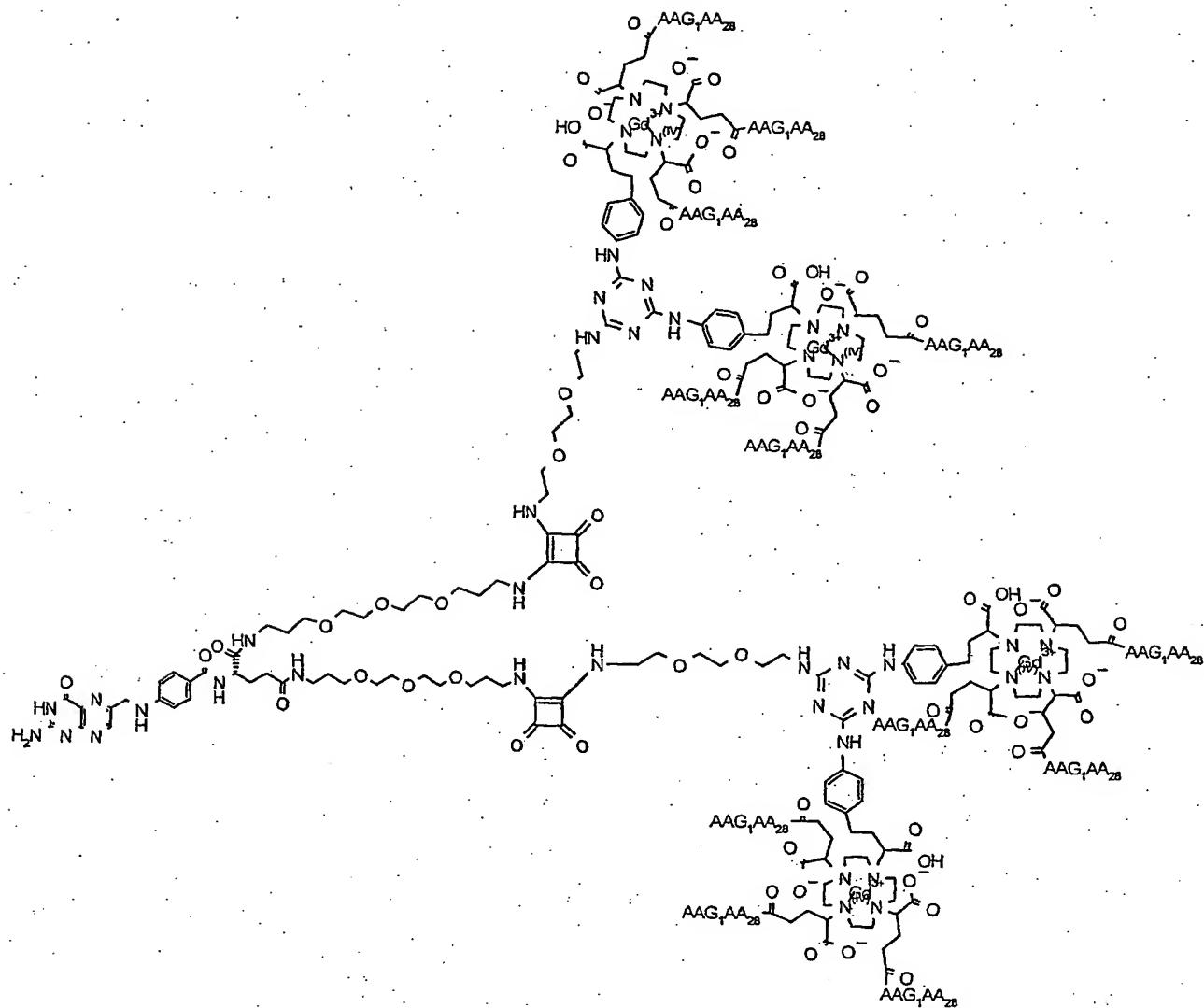
5 24. Compound according to Claim 20, characterized in that G5 is absent, with, preferably, G1 being OH, G2 being NH_2 , G6 being N.

25. Compound according to Claim 20, characterized in that G6 is N or C.

10 26. Compound according to Claim 20, characterized in that (E) is



or



27. Compound according to one of Claims 1 to 19, characterized in that the biovector is an angiogenesis inhibitor.

5

28. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of inhibiting the activity of an MMP.

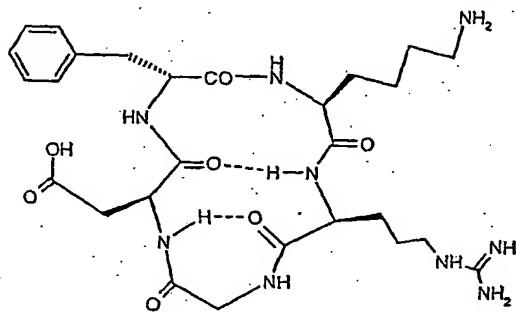
29. Compound according to Claim 28, characterized in that the biovector is an MMP inhibitor derived from ilomastat.

10

30. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting an integrin.

5 31. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting the integrin $\alpha v\beta 3$, in particular an RGD peptide, a peptidomimetic of the RGD peptide, or a non-peptide agent capable of mimicing the action of an RGD peptide.

10 32. Compound according to Claim 31, characterized in that the biovector is an RGDfV peptide having the structure :



33. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting the integrin GPIIb/IIIa.

15 34. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting a vitronectin.

20 35. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting an angiogenic receptor of endothelial cells, in particular a VEGFR receptor, preferably a peptide ATWLPPR or HTMYYHHYQHHL.

36. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting receptors located on macrophages, in particular SRA receptors.

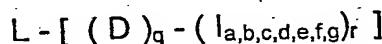
5 37. Compound according to Claim 36, characterized in that the biovector is a derivative of phosphatidylserine.

38. Compound according to one of Claims 1 to 19, characterized in that the biovector is a bisphosphonate derivative.

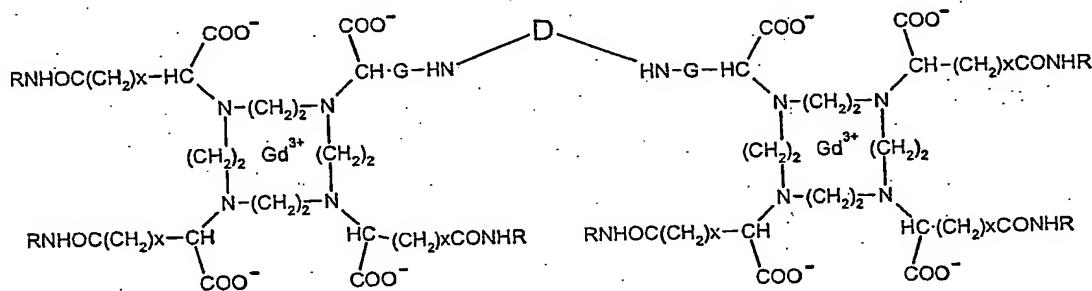
10 39. Compound according to one of Claims 1 to 19, characterized in that the biovector is a peptide targeting tuftsin.

15 40. Compound according to one of Claims 1 to 19, characterized in that the biovector is Annexin 5.

41. Intermediate compound, used for preparing a compound according to Claim 1, of formula:

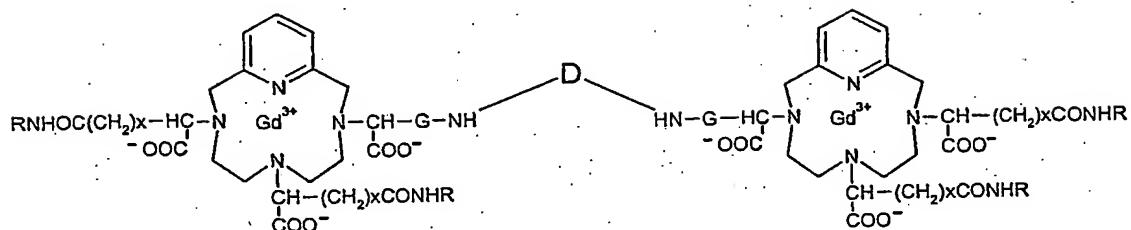
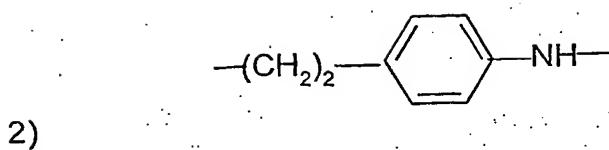


20 with L preferably of squarate type, q=1 and $[(D)_q - (I_{a,b,c,d,e,f,g})_r]$ preferably being chosen from :



11'2

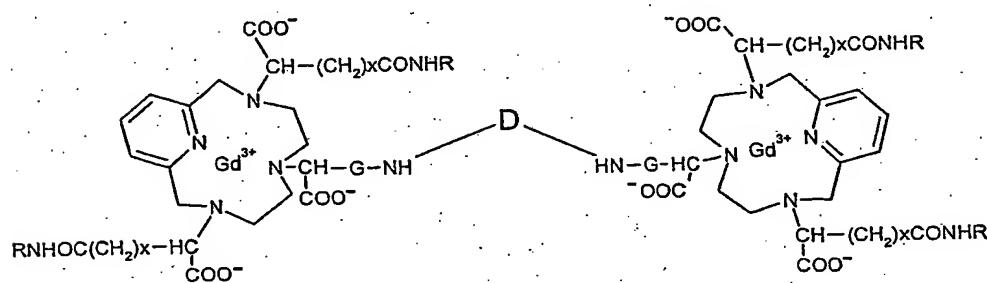
25 with -G-NH being -(CH2)3-NH- or



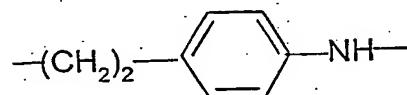
II" a2

5

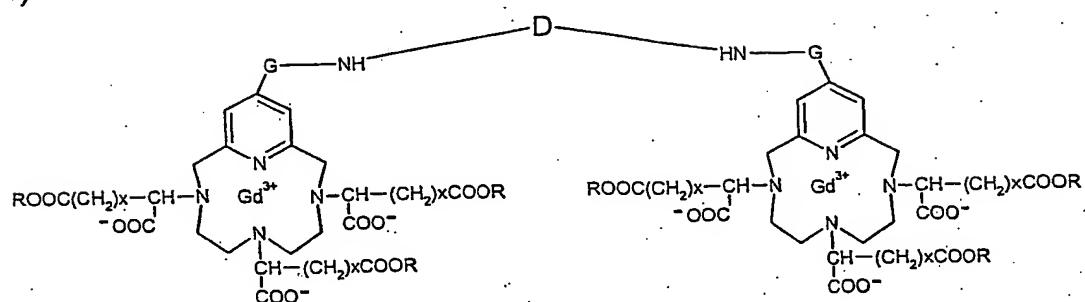
3) II" b2



10 with -G-NH being -(CH2)3-NH- or



4)



II " 2

with G-NH being $-(\text{CH}_2)_3\text{-NH}$.

5 42. Compound according to any one of Claims 1 to 40, in its form bonded to an element M, (E) being written $\text{B}_x - \text{L} - (\text{HR Ch})_y - \text{M}$; given that M is either a paramagnetic metal ion having the atomic number 21-29, 42-44, or 58-70, or a radionuclide, typically chosen from ^{99}Tc , ^{117}Sn , ^{111}In , ^{97}Ru , ^{67}Ga , ^{68}Ga , ^{89}Zr , ^{177}Lu , ^{47}Sc , ^{105}Rh ; ^{188}Re , ^{60}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{90}Y , ^{159}Gd , ^{149}Pr , and ^{166}Ho , or a heavy metal ion having the atomic number 21-31, 39-49, 50, 56-80, 82, 83 or 90.

10 43. Magnetic resonance imaging contrast product, characterized in that it comprises a compound according to one of Claims 1 to 40, optionally combined with a pharmaceutically acceptable vehicle.

15 44. Contrast product according to Claim 43, provided in the form of an injectable sterile solution.

20 45. Compound according to either one of Claims 43 and 44, for its use in the diagnosis of a cardiovascular, cancer-related or inflammatory pathology.

25 46. Nuclear medicine product, characterized in that it comprises a compound according to one of Claims 1 to 38, optionally combined with a pharmaceutically acceptable vehicle.

30 47. Compound according to any one of Claims 1 to 22, having a relaxivity of between 25 and 200 $\text{mM}^{-1}\text{Gd}^{-1}$.

48. Method for preparing a compound according to any one of Claims 1 to 40 characterized in that it comprises the coupling of at least one biovector and at least one high-relaxivity chelate as defined in one of Claims 1 to 18.